The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SVETLANA SHCHEGROVA, WILLIAM O. FISHER, and PETER G. WEBB

Appeal No. 2006-2664
Application No. 10/061,800

ON BRIEF

Before ADAMS, MILLS, and LINCK Administrative Patent Judges.

LINCK, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal from the Examiner's final rejection under 35 U.S.C. § 103(a) of the pending claims 1-33 in Application No. 10/061,800 (hereafter the "'800 application").[1]

The invention on appeal relates to correcting errors in array fabrication by using redundant dispensers in place of error dispensers. There are three independent claims in

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[1] The present application was filed on January 30, 2002 and is assigned to Agilent Technologies, Inc.

the '800 application, claims 1, 6 and 25, from which all other claims depend. Claim 1 is the broadest claim and reads:

> 1. A method of fabricating a chemical array using:
> a head system with multiple groups of drop dispensers;
> a transport system to move the head system with respect to a substrate;
> a processor to dispense droplets from dispensers during operation of the transport system, in a pattern along a selected path for each group;
> the method comprising:
> a) loading the dispensers with fluid such that each dispenser group has at least one set of redundant dispensers loaded with a same fluid;
> b) dispensing drops from the dispensers to identify an error in one or more dispensers;
> c) moving a first dispenser of each set in each group along the selected path for that group while dispensing drops from non-error first dispensers of the sets in at least part of the pattern along the selected path for each group;
> d) moving a second dispenser of the sets in each group along the selected path for that group while dispensing drops from a non-error second dispenser of a set having an identified error first dispenser, in at least part of the pattern for the selected path of the first group; and
> e) repeating (a) through (d) at least once;
> wherein the array is fabricated.

Claims 1-3, 5-19, 21-29 and 31-33 of the '800 Application are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al., U.S. Patent No. 5,807,522 issued Sept. 15, 1998 ("Brown"); and Tisone et al., U.S. Patent No. 6,063, 339 issued May 16, 2000 ("Tisone"). Additionally, dependent claims 4, 20 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown, Tisone, and Gamble et al., U.S. Patent No. 5,958,342 issued Sept. 28, 1999 ("Gamble").

With the authority to adjudicate appeals from final rejections under 35 U.S.C. § 134, we find that the Examiner has not established a prima facie case of obviousness. We reverse the Examiner's rejections of record.

BACKGROUND

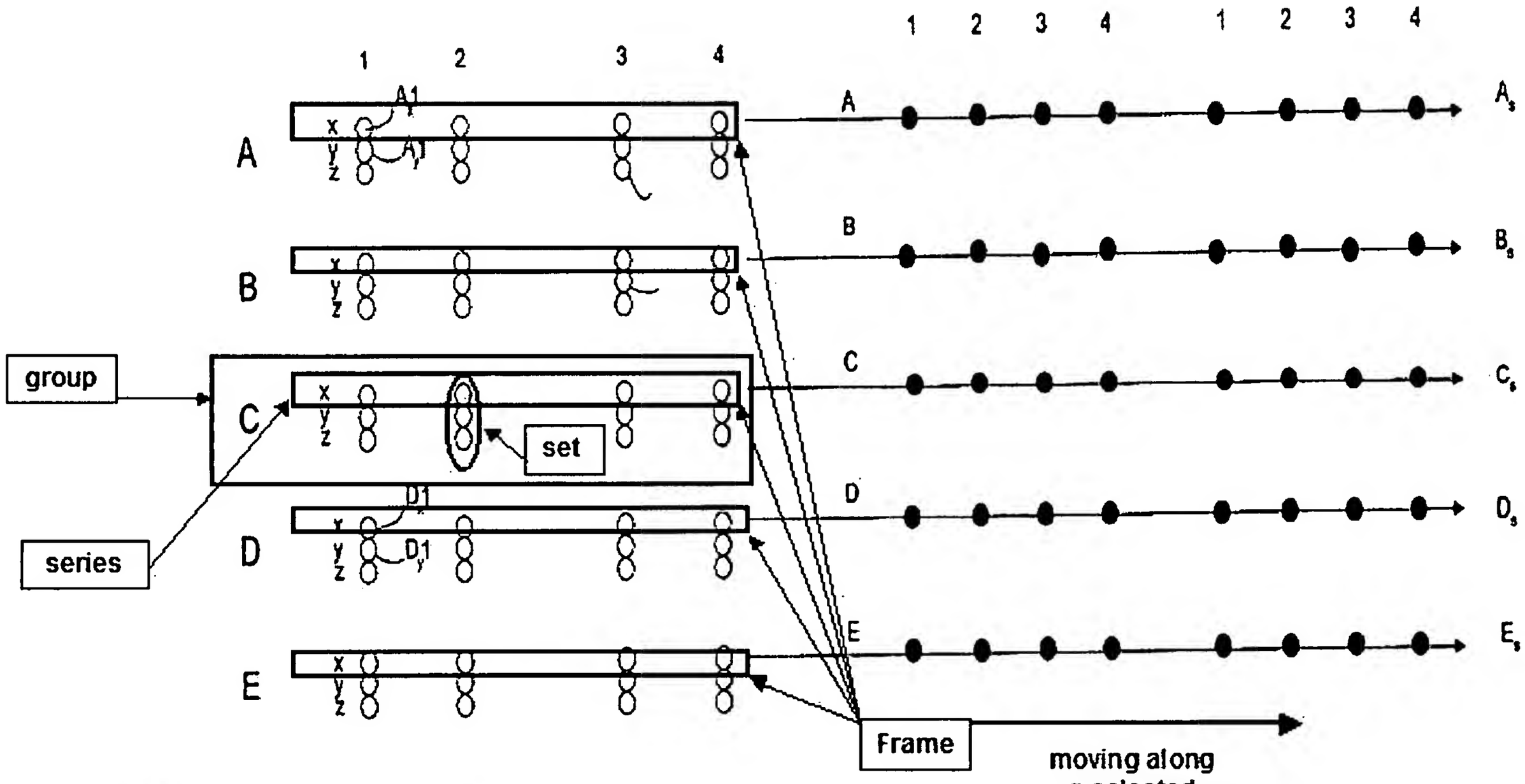
The invention generally "relates to arrays, particularly polynucleotide arrays such as DNA arrays, which are useful in diagnostic, screening, gene expression analysis, and other applications." Specification at 1. The inventors recognized a problem in array fabrications using multiple drop dispensers that move in relation to a substrate to deposit drops, where one or more dispensers may be in error. *Id.* at 3. The inventors also realized that "array quality can still be maintained by providing one or more redundant dispensers and an efficient way of using redundant dispensers in place of error dispensers." *Id.* "Dispensers of each set communicate with a common reservoir for that set" and, in effect, the dispensers of the same set are "loaded with the same fluid" and are "redundant." *Id.* at 12. During array fabrication, a functioning redundant dispenser ("non-error dispenser") is used in place of a previously identified error dispenser of the same set. *Id.*

Accordingly, the claims of the invention set forth methods that utilize a set of non-error redundant dispensers to correct identified error dispensers. The apparatus generally is comprised of a head system with multiple groups of dispensers, a transport system, and a processor. Specification at 3. Reproduced below, Figure 4B of the application shows an exemplary arrangement of "sets," "series," "groups," and "frames" of dispensers and a completed array (hollow circles represent drop dispensers and solid black circles represent deposited drops). The claim terms "sets," "series," "groups," and "frames" help identify particular groupings of dispensers in order to describe movement of dispensers according to the claimed method. Below in the figure, "groups" are marked

as A, B, C, D, and E and rows x, y, and z are "series" within each group. "[A] set of dispensers are those with the same group and column identification" (i.e. column 1, 2, 3, or 4). Specification at 12. For example, dispensers A_x1, A_y1, and A_z1 constitute a set. *Id.* A "frame" of dispensers is a

> shorthand way of designating series of dispensers from different groups of dispensers in a head system, which can simultaneously move along the selected paths for their groups forming a dispenser frame. For example, where the series are lines, the lines from each group which simultaneously move along the selected paths for their groups, form a frame. [*Id.* at 9.]

The methods claimed generally comprise the steps of loading each set of redundant dispensers with the same fluid; dispensing drops from the dispensers to identify an error; moving first dispensers or a frame of first dispensers along a selected path while dispensing only from non-error dispensers, and moving a redundant dispenser or frame with redundant dispensers along the selected path while dispensing drops from non-error redundant dispensers in the same set as the error first dispensers.



*** Note: the captions "group," "series," "set," "frame," and the corresponding arrows have been added for descriptive purposes. ***

FIG. 4B

DISCUSSION

Dependent claims 4, 20 and 30 each add a pulse jet limitation to the dispensers claimed in the aforementioned independent claims. We initially focus on claim 1, the broadest claim in the application.

Concerning the application of § 103(a), the Supreme Court has articulated three factors that are relevant to an obviousness determination: (1) the scope and content of the prior art; (2) the differences between the prior art and claims at issue; and (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 469 (1966). Thus, *Graham* instructs us to consider these three factors prior to turning to the ultimate legal conclusion.

The Scope and Content of the Prior Art

The invention's field of endeavor generally "relates to arrays, particularly polynucleotide arrays such as DNA arrays, which are useful in diagnostic, screening, gene expression analysis, and other applications." Specification at 1. The Examiner relies on two prior art patents (Brown and Tisone) as a basis for rejecting pending claim 1 under 34 U.S.C. § 103(a). Both references relate to the inventors' field of endeavor.

The Brown patent relates to a method and apparatus for fabricating microarrays of biological samples for large scale screening assays. Col. 1, lines 15-17. Brown discloses a "method of forming a microarray of [discrete] analyte-assay regions on a solid support, where each discrete region in the microarray has a selected, analyte-specific reagent . . . ." Col. 3, lines 24-27; col. 19, lines 1-4. Brown discloses a dispensing device (col. 7, lines 2-5), a transport system (col. 7, lines 31-33), a processor to dispense droplets

in a selected pattern (col. 10, line 63- col. 11, line 3), the step of loading a dispenser (col. 7, lines 55-58), and the step of depositing solution onto a surface by tapping the dispensing device against the support (col. 7, line 66 – col. 8, line 3).

Although the Brown reference discloses use of "multiple dispensing heads," (*see* Answer at 10), it does not disclose redundant dispensers as described and claimed by Appellants. Brown discloses that the "dispensing device in the apparatus may be one of a plurality of such devices which are carried on the arm for dispensing *different* analyte assay reagents at selected spaced array positions." Col. 4, lines 12-15 (emphasis added). Thus, the multiple dispensers in Brown are not loaded with the same fluid. Moreover, the Examiner concedes that Brown fails to teach the step of identifying an error dispenser. Answer at 5.

Tisone is the second reference relied upon by the Examiner to reject claim 1. The Tisone patent relates to "a method and apparatus adapted for high-speed, precision dispensing of high-density 'dot' arrays and other patterns onto a receptive membrane, high-density micro-well plate or other suitable receptacle." Col. 1, lines 13-16. Tisone discloses simultaneous dispensing from multiple dispensers of the same fluid in particular arrangements, i.e., in parallel or in another coordinated manner. Col. 7, lines 61-67; col. 22, lines 16-31. Tisone discloses an apparatus with a dispensing head (head system), a pump device, and a controller (processor). Col. 25, lines 40-67; col. 4, lines 22-28; col. 8, lines 18-25. Tisone also discloses that "*multiple dispensing heads* in linear or two-dimensional arrays can also be used with equal or improved efficacy" and "may be provided and operated either *in parallel* as illustrated in Fig. 2 (ie. for multi-gang

operation) *or in another coordinated fashion*, as desired," i.e. independent of one another. Col. 7, lines 61-67 (emphasis added); col. 22, lines 16-18. Furthermore, Tisone discloses the following:

> *Arrays of dispenser heads* could also be configured together... so as to provide array dispensing of 8, 16, or 64 drops *simultaneously* . . . Fig. 2 illustrates a single continuous feed platform . . . configured with *multiple dispensers . . . to handle one* or more *reagents.* This particular dispensing apparatus configuration has significant advantages for continuous web production applications since one or more syringe pumps . . . can be operated in alternating succession while allowing the non-dispensing syringe pump to draw additional reagent from the reservoir or they can be configured independent of one another *to dispense the same or different reagents simultaneously or in succession.*

Col. 22, lines 18-31 (emphasis added). These disclosures in Tisone teach or suggest groups, sets, series, or frames of dispensers and coordinated and simultaneous dispensing.

However, Tisone's disclosure of simultaneous dispensing of multiple dispensers of the same fluid in coordinated arrangements is *unrelated* to any error identification and correction. Tisone involves a method and apparatus for high-speed dot array dispensing that takes place "on-the-fly," i.e., "without the need to alternately stop and start the X-Y carrier platform." Col. 7, lines 35-39; col. 8, lines 25-27.[2] Thus, dispensing occurs while there is continuous motion between the substrate and dispensing head. Col. 4, lines 14-28.

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[2] The '800 Application invention is also "on-the-fly" dispensing because claim elements 1(c-d), 6(c-d), and 25 (c-d) recite steps of moving dispensers or frames *while* dispensing from dispensers. *See* claim 1.

"Phase adjustment," a type of error correction, occurs to "accommodate . . . on-the-fly dispensing without compromising accuracy, precision or repeatability." Tisone, col. 8, lines 25-28. The phase adjustment calculated for each dispense cycle "is such as *to advance (or retard) the timing of the valve opening and closing* so that the dispensed droplet of reagent . . . lands at the desired location on the substrate . . . (or at a desired offset location), taking into account its anticipated trajectory." Tisone, col. 8, lines 30-34 (emphasis added). Phase adjustments can be "determined experimentally . . . either before or during production" and

> will depend, among other things, on a number of system input and output parameters and behavioral characteristics, including the desired drop offset (if any), the vertical distance between the dispensing head nozzle . . . and the surface of the substrate . . . , the velocity and/or acceleration of the dispensing head . . . and/or the substrate . . . relative to one another, the velocity of the dispensed droplets, ambient temperature and humidity, and other controlled and/or uncontrolled factors.

Tisone, col. 8, lines 36-52.

Based on these disclosures, Tisone identifies errors with respect to where dispensed droplets land during on-the-fly dispensing and then corrects these errors by *adjusting* the parameters of the *same* error-dispensers. See, e.g., Tisone, col. 19, lines 6-9. Thus, Tisone fails to teach a method that utilizes the multiple, redundant dispensers for error identification and correction as recited in claim 1 elements 1(c-d), 6(c-d) and 25(c-d).

The Level of Skill in the Art

The level of skill in the art is not challenged and is reflected in the references cited in the case.

The Differences Between the Prior Art and the Claims At Issue

Appellants argue that the Examiner's prima facie case of obviousness is deficient because the combined teachings of the cited prior art fail to teach or suggest all the claim limitations of the rejected claims. Brief at 8. In particular, Appellants argue that Brown and Tisone do not teach or suggest at least the following features:

- "A head system with multiple groups of drop dispensers;"
- Claim element 1(a): the step of "loading the dispensers with fluid such that each dispenser group has at least one set of redundant dispensers loaded with a same fluid;"
- Claim element 1(b): the step of "dispensing drops from the dispensers to identify an error in one or more dispensers;"
- Claim element 1(c): the step of "moving a first dispenser of each set in each group along the selected path for that group while dispensing drops from non-error first dispensers of the sets in at least part of the pattern along the selected path for each group;" and
- Claim element 1(d): the step of "moving a second dispenser of the sets in each group along the selected path for that group while dispensing drops from a non-error second dispenser of a set having an identified error first dispenser, in at least part of the pattern for the selected path of the first group."

Id. at 9, 14, 15. Appellants describe their invention as a "method of fabricating an array [that] utilizes redundant dispensers (i.e., *Sets* of dispensers) in such a way that a drop that was not deposited by a first defective (or error) dispenser of a *Set* is deposited by a second (or third) non defective (or non-error) dispenser of the same *Set*." *Id.* at 11. The

Appellants state that this "configuration of dispensers makes the claimed method possible." *Id.* Essentially, according to Appellants, "Brown et al. and Tisone et al. fail to teach or suggest *Groups, Sets, Series,* or *Frames* of dispensers as is claimed" and "[w]ithout such a teaching, these references simply cannot teach the error correction array fabrication methods of the claimed invention." *Id.* at 19.

Furthermore, Appellants argue that Tisone fails to teach the steps of identifying an error dispenser, withholding dispensing from the error dispenser, and "dispens[ing] fluid from a *second* (or third) non-error (i.e., functional) dispenser selected from the same redundant *Set* in which the error dispenser is found." *Id.* at 14.

We agree with the Appellants' assessment of the differences between the prior art and the claims at issue in that Brown and Tisone, combined, fail to teach a method of error identification and correction that utilizes redundant dispensers as required by claim 1 steps (a)-(d).

The § 103(a) Determination in View of These Graham Findings

The issue before us is whether the evidence of record supports the Examiner's prima facie case of obviousness. In order to establish a prima facie case of obviousness, there must be "some objective teaching in the prior art or . . . knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant teachings of the references." *In re Fine,* 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In some circumstances, a single prior art reference can render a claim obvious if there is "a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness

conclusion." *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000). Evidence of a suggestion, teaching, or motivation to combine or modify may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or from the nature of the problem solved. *In re Kahn,* 441 F.3d 977, 987-88, 78 USPQ2d 1329, 1338 (Fed. Cir. 2006); *SIBIA Neurosciences*, 225 F.3d at 1356, 55 USPQ2d at 1931.

The invention's error correction method requires step b, the identification of error dispensers; step c, dispensing only from non-error dispensers on the initial pass; and step d, on subsequent passes, dispensing from *redundant* non-error dispensers loaded with the same fluid as the error dispensers that did not function on the first pass. These three steps require the loading of redundant dispensers (step a). None of these steps is disclosed by the cited prior art.

With respect to claim 1, the Examiner applies Brown as being directed to an apparatus with a positioning structure (transport system), a dispensing structure (head system) with a dispensing device for depositing a fluid onto the surface of the substrate, and a control unit (processor) that controls the positioning and dispensing; and a method comprised of loading the dispenser with a reagent solution, moving the dispenser to a selected position with respect to a support surface, dispensing the solution reagent onto the surface of the substrate, and repeating the steps to produce an array. Answer at 4-5 (citing Brown, col. 3, line 59 – col. 4, line 15; col. 4, lines 12-15.; col. 7, lines 55-65; col. 9, lines 5-10, col. 10, line 63 - col. 11, line 28).

The Examiner acknowledged that Brown is missing the step of identifying an error dispenser. Answer at 5. To address this deficiency, the Examiner looks to Tisone, which discloses determination of a phase adjustment by the controller for each dispense cycle either before or during production such that a high degree of accuracy, precision, and repeatability is attained. Answer at 5 (citing Tisone, col. 8, lines 48-55).

The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time of the invention to include the step of identifying an error dispenser as taught by Tisone in the method of Brown. Answer at 5. Moreover, the Examiner states one of ordinary skill in the art would have been motivated to include the step of identifying an error dispenser in the method of Brown for the advantage of providing an apparatus dispenser system with a control system that precisely coordinates dispensing operations with a high degree of accuracy, precision, and repeatability. *Id.* at 5.

Furthermore, in response to Appellants' argument that neither Brown nor Tisone teaches or suggests at least one set of redundant dispensers in each group of dispensers and claimed steps 1(c) and 1(d), the Examiner maintains that Brown and Tisone suggest the limitations of claim 1 because a group of dispensers can be a single row of dispensers and a set can be just one dispenser. *Id.* at 10-11. The Examiner supports their argument by citing the specification's definition of a "set" or "sub-set" of any item, which can include just one of the items. *Id.* at 11 (citing Specification at 8).

We find the Examiner's position to be inconsistent with the claim language. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to

which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312, 75 USPQ2d 1321, 1325 (Fed. Cir. 2005) (citations omitted). "Quite apart from the written description and the prosecution history, the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Id.* at 1314, 75 USPQ2d at 1327 (citations omitted). For example, "the use of a term within the claim provides a firm basis for construing the term." *Id.* Additionally, claims "must be read in view of the specification, of which they are a part." *Id.* at 1315, 75 USPQ2d at 1327. "Of course, at all times, the language of the claims governs their scope and meaning" and "[u]nless the intrinsic evidence compels a contrary conclusion, the claim language carries the meaning accorded those words in the usage of skilled artisans at the time of invention." *Smithkline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1338-39, 74 USPQ2d 1396, 1403 (Fed. Cir. 2005).

The Examiner has taken the claim term "set" out of the context of the claim. Here, claim 1 reads in part:

- Claim element 1(a): the step of "loading the dispensers with fluid such that each dispenser group has at least one *set of redundant dispensers* loaded with a same fluid;"
- Claim element 1(c): the step of "moving a first dispenser of each set in each group along the selected path for that group while dispensing drops from non-error first dispensers of the sets in at least part of the pattern along the selected path for each group;" and
- Claim element 1(d): the step of "moving *a second dispenser* of the sets in each group along the selected path for that group while dispensing drops from *a non-error second dispenser of a set having an identified error first dispenser*, in at least part of the pattern for the selected path of the first group."

(Emphasis added). This claim language makes clear that it *requires* a dispenser group with at least one "set of *redundant* dispensers." The specification states that dispensers within a set are "redundant in that one can be used *in place of the other* during array fabrication (assuming the one used in place is functioning and is not in error in some way)." Specification at 12 (emphasis added). Redundancy of dispensers necessarily requires at least one dispenser *redundant to another*. The specification defines a "set" or "subset" of any item as containing "only one of the item, or only two, or three, or any number of multiple items." Specification at 8. Thus, we find that a "set of redundant dispensers" can be one, two, or three, or any number of dispensers *redundant to another.*

We agree with Appellants that "a '*set*' of dispensers as recited in Claim 1 **must** have more than one dispenser to perform the claimed methods" and this limitation is clear from reading the claims. Reply at 2. As indicated by Appellants, the "only way that [a second dispenser in a set could dispense drops where error dispensers did not] is for a *set* of dispensers to have more than one dispenser" and "a *set* of dispensers as claimed in Claim 1 **must** have at least two dispensers." Reply at 3.

Claim 1

After careful review of the Brown and Tisone patents, we find that the combined or modified teachings of the references fail to teach a method of error identification and correction that utilizes redundant dispensers. Brown does not add anything to the Examiner's argument for prima facie obviousness. Moreover, although Tisone teaches a head system with multiple groups of drop dispensers containing the same fluid, arranged in a coordinated fashion, and discloses error identification through experimentation,

Tisone fails to teach a method that utilizes the multiple, redundant dispensers for error correction as recited in claim elements 1(c-d), 6(c-d) and 25(c-d).

Rather, we agree with Appellants that

> the error identification method disclosed in Tisone et al. is directed to controlling specific parameters of valve deposition (e.g., timing) and does not teach identifying an error dispenser and dispensing only from non-error dispensers during array fabrication as is claimed. Instead, the deposition error method of Tisone et al. evaluates whether a drop is deposited in the desired location and, if it is not, adjustments are made to the parameters of valve deposition to correct it. In other words, there is no such thing as an "error dispenser" in Tisone et al. as claimed in the subject application. If a dispenser deposits erroneously, the method disclosed in Tisone et al. adjusts the parameters of dispensation and deposits fluid using the *same* dispenser.

Brief at 14.

Claims 2-33

Claims 2-33 all require redundant dispensers. Thus, we reverse the rejection of these claims for the reasons we reverse the rejection of claim 1. See our analysis *supra* at pp. 11-16.

Although the Examiner separately rejected dependent claims 4, 20, and 30 under § 103(a) as being unpatentable over Brown, Tisone, and Gamble, we reverse the rejection of these claims without further analysis. Gamble does not disclose or suggest redundant dispensers as claimed and therefore does not resolve the deficiencies of the § 103(a) rejection of the relevant independent claims (1, 6, and 25) from which claims 4, 20,and 30 depend, respectively. The Examiner's rejections for claims 2-33 are reversed.

Other issues

The following printer technology prior art references may be reasonably pertinent to the inventors' use of redundant dispensers to correct for error dispensers:

- Kumar et al., U.S. Patent No. 6,283,572 issued Sept. 4, 2001, for "Dynamic Multi-Pass Print Mode Corrections to Compensate for Malfunctioning Inkjet Nozzles" (Figure 7, Tables I and II, in particular);
- Anderson, U.S. Patent No. 6,076,910 issued June 20, 2000, for "Ink Jet Printing Apparatus having Redundant Nozzles" (claim 13, in particular); and
- Hackleman, U.S. Patent No. 5,640,183 issued June 17, 1997, for "Redundant Nozzle Dot matrix Printheads and Method of Use."

It would have been reasonable for one skilled in the art to look to the field of printer technology at the time of invention given that microarray production companies were innovating with concepts borrowed from printer technology as early as 1998:

- Industrial Technology Research Institute News Release "Implementation of Phalanx Microarray Technology—Fruition of ITRI's Multidisciplinary Effort in Biotechnology," http://www.itri.org.tw/eng/news/spotlight-show.jsp?path=f-20030409.dcr
- ArrayJet History, http://www.arrayjet.co.uk/about.html;
- MacBeath, "Printing Proteins as Microarrays for High-Throughput Function Determination," *Science*, New Series, col. 289, No. 5485 (Sep. 8, 2000), pp. 1760-1763.
- Shimadzu Biotech Press Release October 2001, "Proteome Systems and Shimadzu Biotech Complete 1st Stage of the Chemical Printer Development," http://www.shimadzu-biotech.net/pages/news/1/press_releases/2001_10_a_proteome.php;

(Copies of the internet articles are included in the Appendix.) The Examiner should consider these references before the application is allowed to issue as a patent.

REVERSED

DONALD E. ADAMS
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

NANCY J. LINCK
Administrative Patent Judge

BOARD OF PATENT
APPEALS AND
INTERFERENCES

APPENDIX

News Releases
- Industrial Commentary
- News from English Publications about ITRI
- News Archives
- Spotlight Archives

Implementation of Phalanx Microarray Technology-

- Fruition of ITRI's Multidisciplinary Effort in Biotechnology

Background

The research field of molecular biology began with the discovery of DNA structure in 1953, and has gained a great wealth of knowledge and revolutionized the study of biology and medicine. The more application-oriented side is biotechnology, which in recent years has caught the world's attention as a steady stream of success stories on cloning, genetic modification and human genome project appears in the news. Researchers in biotechnology are continuously searching for devices and methods with better precision and higher throughput.

DNA Microarrays

With the availability of whole genome sequences, many tools were developec to study biology on a whole-genome scale. The DNA Microarray, or Gene Chip, is the most important invention of them all. A DNA microarray is a slide (a few square centimeters) that contains many different kinds of DNA (called "probes") deposited on its surface, each based on a certain gene from a genome of interest. The probes on the slide usually are arranged in an array, each address (or spot) on the DNA microarray corresponds to a specific gene. The probe on the slide can grab or "hybridize with" the complementary DNA or RNA fragments (called "targets") generated from the testing sample. By measuring the fluorescent intensity on a probe location after hybridization, one can estimate the expression activity of a specific gene in the testing sample.

Manufacturing Processes for DNA Microarrays

Currently there are two basic ways of making DNA microarrays: the in-situ

synthesis and the spotting methods.
The in-situ method performs the direct synthesis of DNA molecules on the surface of the microarray slide. Tens of thousands of DNA synthesis reactions are carried out simultaneously on the slide surface. There are two different in-situ synthesis methods, i.e., photolithography and inkjet printing. The photolithography method borrows technology developed in the semi-conductor industry. A series of specially designed photo-masks are used to introduce in sequence the photoactive analogs of the four DNA nucleotides (A, C, T, and G) into the synthesis reactions. The other in-situ method uses the inkjet printing mechanism to deliver the DNA nucleotides onto the probe location. The inkjet-head movement is computer-controlled to ensure the accuracy of the nucleotide deposition process. For both methods, the quality of the DNA is very difficult to monitor or control. They also suffer from high manufacturing cost and low production capacity. The unit price ranges from US$500 to US$2,000.
In the spotting method, the probes are synthesized before they are applied to the microarray surface. The probe is usually synthesized by polymerase chain reaction (for the longer cDNA probe) or by a conventional DNA synthesis method. The probes are then spotted on the slide and immobilized through various surface chemistry mechanisms. The effectiveness of this method is highly dependent on the design of the arraying equipment and the surface chemistry between the probe solution, the dispensing apparatus, and the slide surface.
Currently there are many robotic microarrayers and microarray slides available on the market for smaller scale production. The systems are usually set up by the microarray core facility of research institutes for in-house usage. The throughput and the production size are relatively low, so the unit cost stays high. The quality of the microarrays is inconsistent, making comparison between various microarray experiments very difficult if not impossible. ITRI has now come up with a manufacturing scheme that combines the advantages of in-situ and spotting methods, resulting in significantly higher throughput and lower cost.

ITRI's Phalanx Microarray Technology - a High Throughput Manufacturing Process

In 1998, theBiomedical Engineering Center (BMEC)of ITRI initiated the Biochip Project to explore the potential of microarray technology. The multidisciplinary research team of the project came from 5 different research ITRI divisions, including BMEC,Opto-Electronics & Systems Laboratories (OES),Center for Measurement Standards (CMS),Union Chemical Laboratories(UCL), andElectronics Research & Service Organization (ERSO). The project has led to a multitude of patents, covering the subjects of surface chemistry, microdispenser, microarray, and electrophoresis. The collective result of the project is the phalanx microarray technology, which is a high throughput manufacturing process that can produce reliable, high-quality microarrays with a density of 4,000 pre-synthesized probes per cm2 at low cost, perhaps as low as one-tenth of that of the current product

The core of the phalanx microarray technology is the Phalanx Jet liquid micro-dispenser, Phalanx Arrayer, and Phalanx Slide. The Phalanx Jet and Phalanx Array were co-developed by BMEC and OES. The Phalanx Jet

employs bubble jet printer technology to precisely dispense micro-volume liquid at very high density. The Phalanx Arrayer is an automatic arraying platform that can be assembled into a continuous arraying pipeline with high precision and throughput. BMEC and UCL co-developed the surface chemistry for the Phalanx Slide that enables the DNA solution to maintain a uniform contact surface and to maximize the DNA immobilization on the slide surface.

The Founding of Phalanx Biotechnology Group, Inc.

Due to the great success of the Biochip Project, ITRI and other local biotech businesses formed the Biochip R&D Alliance to pursue the accompanying commercial opportunities. To make the best use of the Project's IP, ITRI put together an IP bundle and licensed it exclusively to the new start-up formed by that Alliance. The Alliance has invested an aggregate of 500 million NT dollars to create Phalanx Biotech Group, Inc. (PBG) to implement the micro-array production technology, staffed mainly by members from the Project.

PBG will have a pilot product Phalanx Human Liver 2000 Microarray, which contains about 2000 probes for liver related genes, by April 2003. It will begin producing Phalanx Human Whole-Genome Microarray (PHWGM), containing more than 30,000 probes that cover all known genes in human genome, by the end of 2003. PBG will design all the probe sequences collaboratively with ITRI using BMEC's bioinformatics software, which will incorporate the most updated human genome information. PBG will also continue to work with BMEC to adopt state-of-the-art quality control concepts into microarray production, such as using MALDI-TOF mass spectrometry to validate the integrity and identity of every probe on the microarray. Furthermore, PBG will continue to work in partnership with other ITRI divisions for the improvement in phalanx microarray technology.

Related Link: http://www.bmec.itri.org.tw/english/main.htm

▲To top of page
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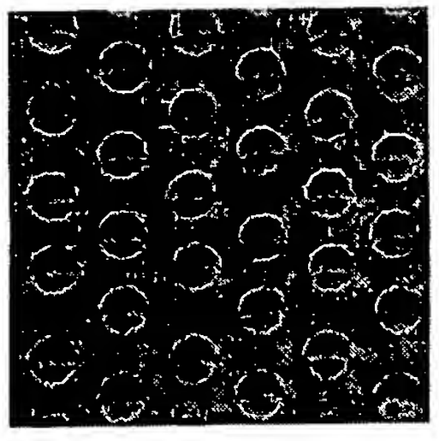
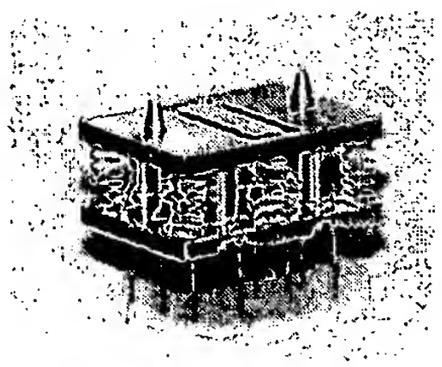
Aj Arrayjet

High Quality Microarray Production Powered by Ink Technology





History

Arrayjet ® Ltd was founded in August 2000 by a Cambridge physicist, Dr. Howard Manning, and University of Edinburgh molecular biologists, Prof. Peter Ghazal and Dr. Douglas Roy, to develop robotics using ink jet printheads to make biological microarrays. In February 2001 Arrayjet secured two-stage funding from the Scotland based investor group known as Archangels and won a Scottish Enterprise SMART award to develop the ink jet microarray platform. Further funding by Archangels and SE followed.

Dr. Manning is Arrayjet's Technical Director and Keith Howell, an Edinburgh based director and consultant, is Chairman. Professor Ghazal is chief scientific advisor and Dr Roy is lead advisor on microarrays. Five engineers have been recruited, premises located close to Edinburgh and a laboratory set up, and professional alliances have been formed.

Arrayjet was at first engaged in product development. In the period from February 2001 to the end of the year the fundamental technology behind Arrayjet was demonstrated, and milestones set by Archangels for the first round of funding were met. Subsequent funding supported the design, manufacture and commissioning of a pre-production prototype.

Arrayjet has now launched a number of products into the microarray market and continues to develop the technology.

ARRAYJET is not licensed under any patents owned by Oxford Gene Technology Limited or related companies ("OGT") and cannot pass any such licence to its customers. A licence under OGT's patents may be necessary to manufacture or use oligonucleotide arrays.

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